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Ziftomenib in Combination with Venetoclax and Azacitidine in Newly Diagnosed *NPM1*-m Acute Myeloid Leukemia: Phase 1b Results from KOMET-007

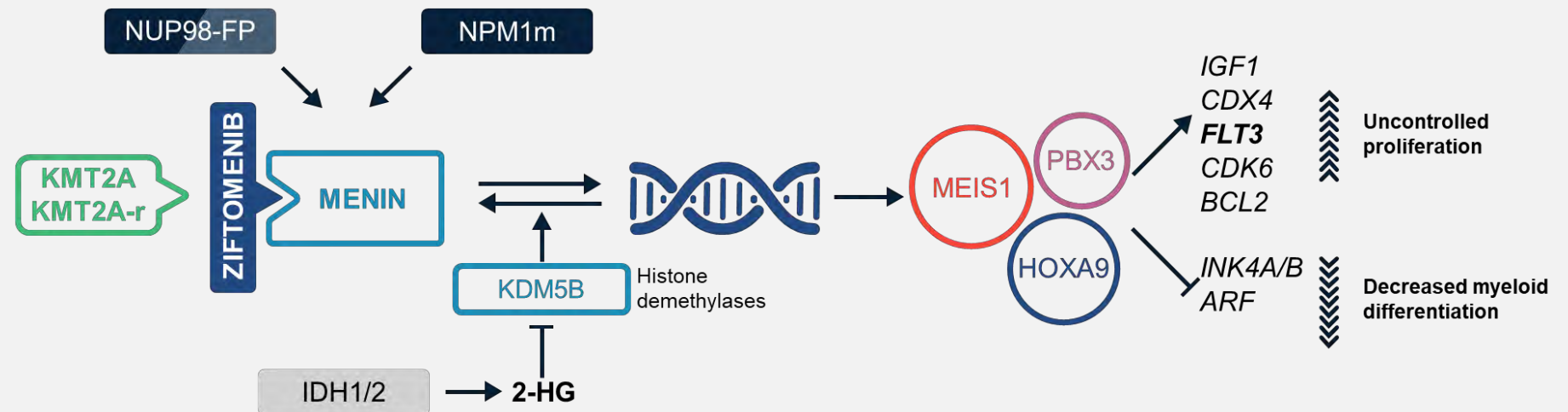
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Ziftomenib Targets the Menin Pathway, a Foundational Target in AML

- *NPM1* mutations drive leukemogenesis in ~30% of AML^{1,2}
- **Ziftomenib** is a potent, highly selective, oral menin inhibitor with clinical activity as both monotherapy and in combination for adults with *NPM1*-m AML^{3,4}
- Ziftomenib monotherapy was approved for R/R *NPM1*-m AML by the [US FDA](#) on November 13, 2025
- **KOMET-007** ([NCT05735184](#)) is an ongoing, global, dose-escalation (phase 1a) and expansion (phase 1b) study of ziftomenib in combination with venetoclax/azacitidine (Ven/Aza), Ven alone, or cytarabine/daunorubicin (7+3) with or without quizartinib in newly diagnosed and relapsed/refractory *NPM1*-m or *KMT2A*-r AML

Ziftomenib Mechanism of Action⁵⁻¹⁴

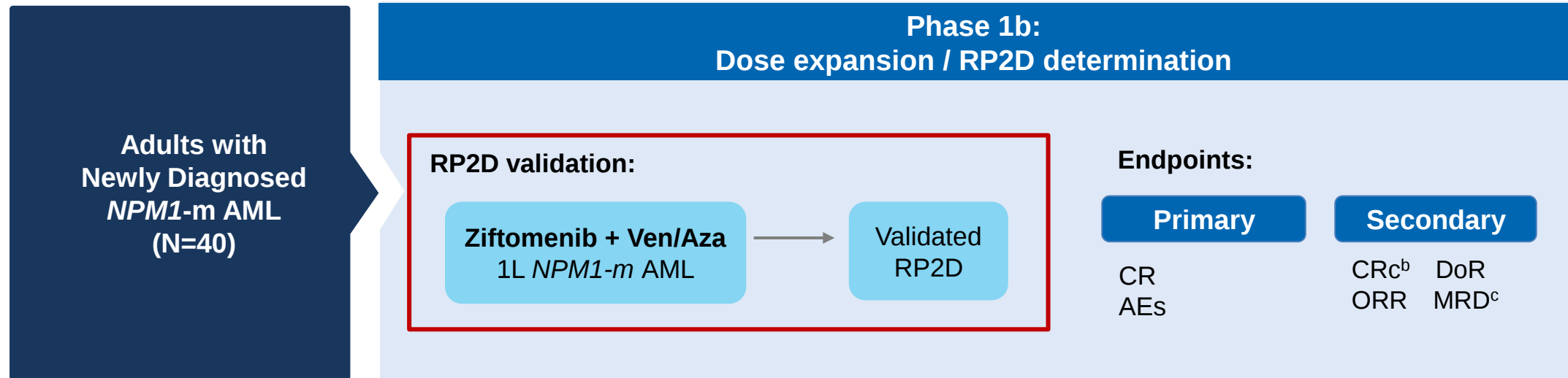


1. Papaemmanuil E et al. *N Engl J Med*. 2016;374(23):2209–21. 2. Issa GC et al. *Leukemia*. 2021;35:2482–95. 3. Wang ES et al. *Lancet Oncol*. 2024;25(10):1310–24. 4. Zeidan AM et al. *Blood*. 2024 Nov 5;144(Suppl_1):214. 5. Collins CT and Hess JL. *Curr Opin Hematol*. 2016;23(4):354–61. 6. Lu R et al. *Cancer Cell*. 2016;30(1):92–107. 7. Ferreira HJ et al. *Oncogene*. 2016;35(23):3079–82. 8. Jeong M et al. *Nat Genet*. 2014;46(1):17–23. 9. Wang GG et al. *Blood*. 2005;106(1):254–64. 10. Chowdhury R et al. *EMBO Rep*. 2011;12(5):463–9. 11. Schmidt L et al. *Leukemia*. 2019;33(7):1608–19. 12. Xu H et al. *Cancer Cell*. 2016;30(6):863–78. 13. Brunetti L et al. *Cancer Cell*. 2018;34(3):499–512. 14. Wang XQD et al. *Cancer Discov*. 2023;13(3):724–45

AML, acute myeloid leukemia; R/R, relapsed/refractory; US FDA, U.S. Food and Drug Administration

KOMET-007: Ongoing Phase 1 Combination Trial of Ziftomenib in Newly Diagnosed AML^a

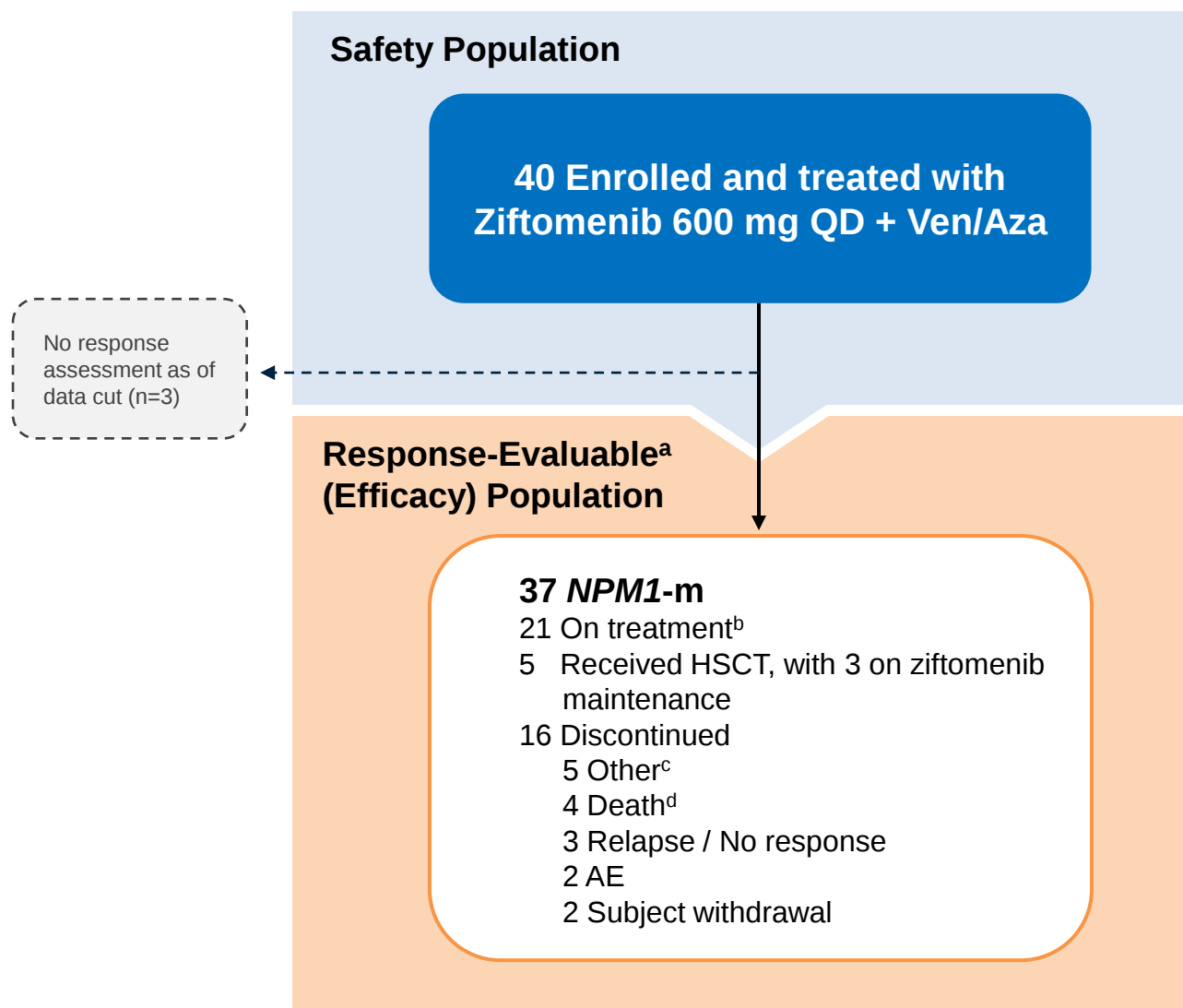
Ziftomenib + Ven/Aza Combination ([NCT05735184](#))



- Ziftomenib dosing started on Cycle 1 Day 8 and was administered continuously thereafter
- Ven was administered per label in 28-day cycles, with adjustments to Ven dosing and cycle length based on blast clearance in Cycle 1 bone marrow biopsy, performed between Days 14–28
- Aza was administered on Cycle 1 Days 1–7
- Patients were treated with ongoing cycles of triplet therapy based on protocol-mandated bone marrow biopsy results
- **Here we present the first safety and clinical activity results in patients with newly diagnosed *NPM1*-m AML from phase 1b treated with ziftomenib 600 mg in combination with Ven/Aza**

^aPatients with *NPM1*-m AML from this cohort were included in the current analysis. ^bCR with full, partial, or incomplete hematologic recovery; ^c*NPM1* MRD was performed by central next-generation sequencing with 5x10⁻⁵ sensitivity 1L, first-line; AE, adverse event; CR, complete remission; CRc, composite complete remission; DoR, duration of response; MRD, measurable residual disease; ORR, objective response rate; RP2D, recommended phase 2 dose

KOMET-007: Safety and Efficacy Populations: Newly Diagnosed AML



- As of Sep 24, 2025, 40 patients with newly diagnosed *NPM1*-m AML were enrolled and treated with ziftomenib 600 mg orally once daily + Ven/Aza
- Median follow-up was **26.1 weeks** (range 1.6–54.1)
- 70% (26/37) of patients were still on-study and 55% (21/37) were still receiving ziftomenib

^aPatients who had ≥1 response assessment or who had died. ^bPatients who had not discontinued ziftomenib as of the data cutoff date. ^cOther reasons included: patient decision for hospice / close to home (n=2), non-compliance (n=1), moved to transplant on local maintenance protocol (n=1), physician decision (n=1). ^dDeaths included: sepsis (n=3), acute respiratory failure (n=1)

Data cutoff: Sep 24, 2025. HSCT, hematopoietic stem cell transplant; QD, once daily

Baseline Characteristics: Newly Diagnosed AML

n (%)	<i>NPM1</i> -m, 600 mg (N=40)
Median age, years (range)	75 (53–93)
Female	21 (53)
Race	
White	31 (78)
Non-White / Other	5 (13)
Unknown / Not reported	4 (10)
ECOG PS	
0	1 (3)
1	16 (40)
2	23 (58)
Selected co-mutations ^a	26 (65)
<i>FLT3</i>	14 (35)
<i>IDH1/2</i>	9 (23)
Therapy-related AML	0 (0)

^aCo-mutations can be co-occurring

Safety and Tolerability of Ziftomenib with Ven/Aza: Newly Diagnosed AML

TEAEs in ≥25% of Patients

n (%)	All TEAEs (N=40)	Ziftomenib-Related TEAEs (N=40)
Any Grade	40 (100)	25 (63)
Nausea	16 (40)	9 (23)
Vomiting	16 (40)	4 (10)
Diarrhea	16 (40)	5 (13)
Fatigue	16 (40)	8 (20)
Thrombocytopenia ^a	15 (38)	8 (20)
Neutropenia ^b	15 (38)	9 (23)
Leukopenia ^c	12 (30)	5 (13)
Constipation	12 (30)	2 (5)
Edema peripheral	11 (28)	2 (5)
Anemia	10 (25)	5 (13)
Aspartate aminotransferase increased	10 (25)	7 (18)
Decreased appetite	10 (25)	6 (15)

- Ziftomenib's safety profile in combination with Ven/Aza appeared similar to that reported for newly diagnosed AML patients treated with Ven/Aza alone¹

^aIncludes platelet count decreased and thrombocytopenia. ^bIncludes neutrophil count decreased and neutropenia; ^cIncludes white blood cell count decreased and leukopenia

1. DiNardo CD et al. *N Engl J Med* 2020;383:617–39

Data cutoff: Sep 24, 2025. TEAE, treatment-emergent adverse event

Safety and Tolerability of Ziftomenib with Ven/Aza: Newly Diagnosed AML

Grade ≥3 TEAEs in ≥10% of Patients

n (%)	All Grade ≥3 TEAEs (N=40)	Grade ≥3 Ziftomenib-Related TEAEs (N=40)
Grade ≥3	34 (85)	16 (40)
Neutropenia ^a	15 (38)	8 (20)
Thrombocytopenia ^b	11 (28)	7 (18)
Leukopenia ^c	10 (25)	4 (10)
Anemia	8 (20)	5 (13)
Febrile neutropenia	5 (13)	1 (3)
Sepsis	5 (13)	1 (3)
Lymphocytopenia ^d	4 (10)	1 (3)
Pneumonia	4 (10)	0 (0)

Ziftomenib-Related AEs of Interest

- 1 (3%) case of differentiation syndrome (grade 2) successfully resolved with protocol-specified mitigation, and patient resumed ziftomenib
- 1 (3%) case of investigator-assessed QTc prolongation (grade 3) occurred in setting of concomitant significant electrolyte abnormalities; event resolved with electrolyte repletion, and patient successfully resumed ziftomenib

Clinical Activity^a of Ziftomenib with Ven/Aza: Newly Diagnosed AML

n (%)	<i>NPM1</i> -m, 600 mg (N=37)
CRc	32 (86)
Median time to first CRc, weeks (range)	3.4 (2.4–9.6)
ORR	33 (89)
CR	27 (73)
CRh	2 (5)
CRi	3 (8)
MLFS	1 (3)
PR	0 (0)
NR	1 (3)
NE^b	3 (8)

- CR/CRh rates by co-mutated status were consistent with overall CR/CRh response rates:
 - 77% (10/13) for *FLT3* and 89% (8/9) for *IDH1/2*

^aIn patients with ≥1 response assessment or had died. ^bPost-baseline response assessment not done (n=3) at time of data cutoff

Data cutoff: Sep 24, 2025. CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not evaluable; NR, no response; ORR, objective response rate; PR, partial response

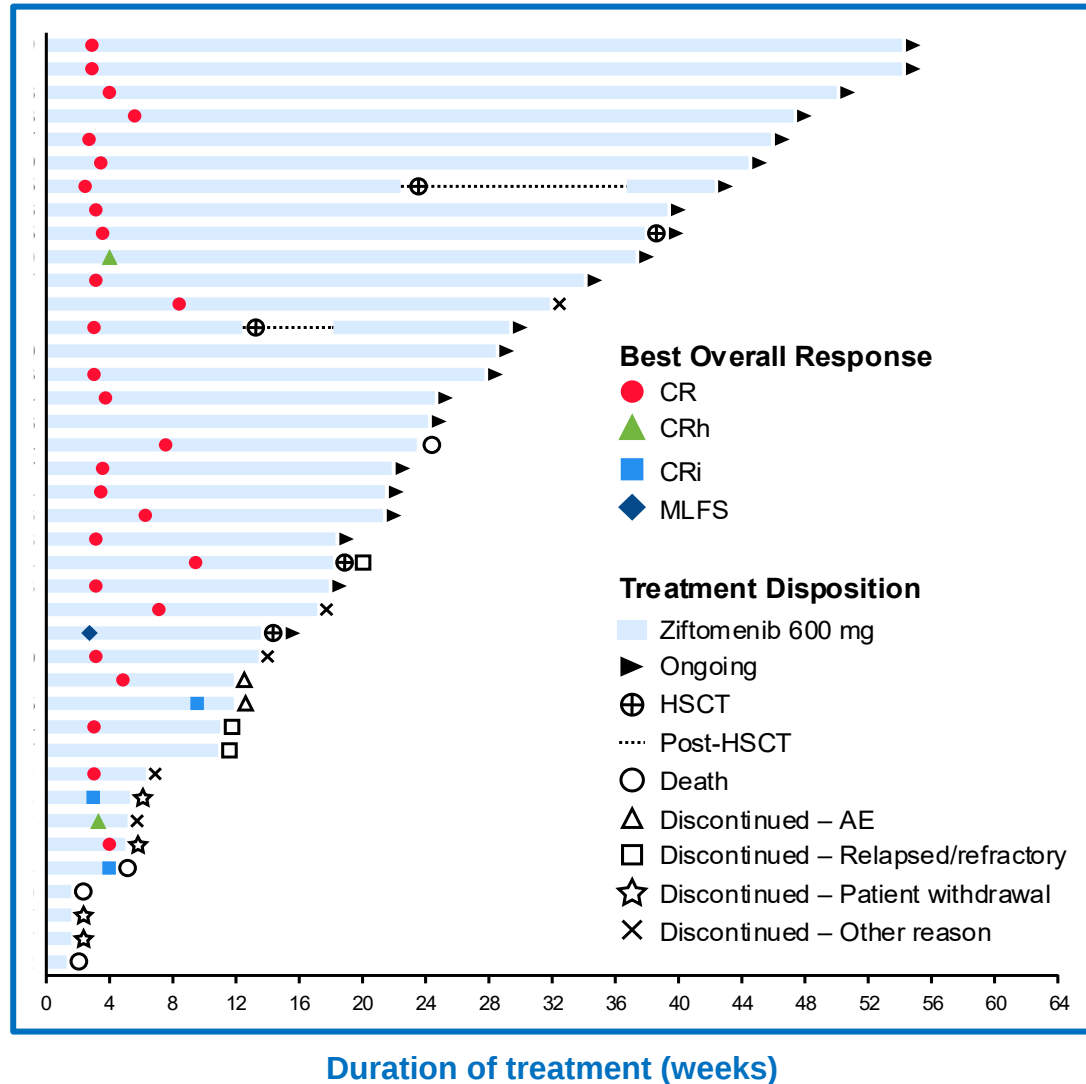
Molecular MRD Negativity in CRc Responders: Newly Diagnosed AML

n/N (%)	Central MRD (Threshold ≤0.1%)	Central MRD (Threshold ≤0.01%)
MRD negativity rate ^a	17/25 (68)	11/25 (44)
Median time to first MRD negativity, weeks (range)	9.4 (4.9–22.9)	9.6 (8.4–22.9)
Timing of MRD negativity ^b :		
By Cycle 1	1/17 (6)	0
By Cycle 2	12/17 (71)	7/11 (64)
By Cycle 3	16/17 (94)	10/11 (91)
By Cycle 4 ^c	17/17 (100)	11/11 (100)

^a*NPM1* MRD was performed among tested CRc responders by central next-generation sequencing with 0.005% sensitivity; protocol-defined threshold ≤0.01% was considered meaningful. ^bAmong CRc responders who achieved MRD-negativity. ^cFour patients who received less than 4 cycles of therapy were just above the 0.01% MRD threshold at time of analysis; MRD assessments are ongoing
Data cutoff: Sep 24, 2025. MRD, measurable residual disease

Duration of Treatment and Clinical Outcomes: Newly Diagnosed AML

NPM1-m



After a median follow-up of 26.1 weeks (range 1.6–54.1):

- Median duration of CR was **not reached**^a
- Median OS was **not reached**^a
- 5 *NPM1*-m patients underwent HSCT, and 3 went onto ziftomenib maintenance
- 68% (27/40) of patients remained alive and continued on-study^b

^aAmong response-evaluable patients; ^bPatients on-treatment or in long-term follow-up

Data cutoff: Sep 24, 2025

CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission; MLFS, morphologic leukemia-free state; HSCT, hematopoietic stem cell transplant; OS, overall survival; PR, partial response

ANC and Platelet Recovery in CRc Responders: Newly Diagnosed AML

Median (range)	<i>NPM1</i> -m, 600 mg (N=32) ^a
Days to ANC recovery $\geq 0.5 \times 10^9/\text{L}$	36 (1–69)
Days to ANC recovery $\geq 1.0 \times 10^9/\text{L}$	37 (1–69)
Days to platelet count recovery $\geq 50 \times 10^9/\text{L}$	24 (0–84)
Days to platelet count recovery $\geq 100 \times 10^9/\text{L}$	30 (20–77)

- Times to neutrophil and platelet count recovery were comparable to those for Ven/Aza alone^{1–3}

^aSubset of patients who reached cutoff

1. Gutman JA et al. *Haematologica*. 2023;108(10):2616–25. 2. Li X et al. *Invest New Drugs*. 2025;43(4):915–23. 3. Rausch CR et al. *Cancer*. 2021;127(14):2489–99

Data cutoff: Sep 24, 2025. ANC, absolute neutrophil count

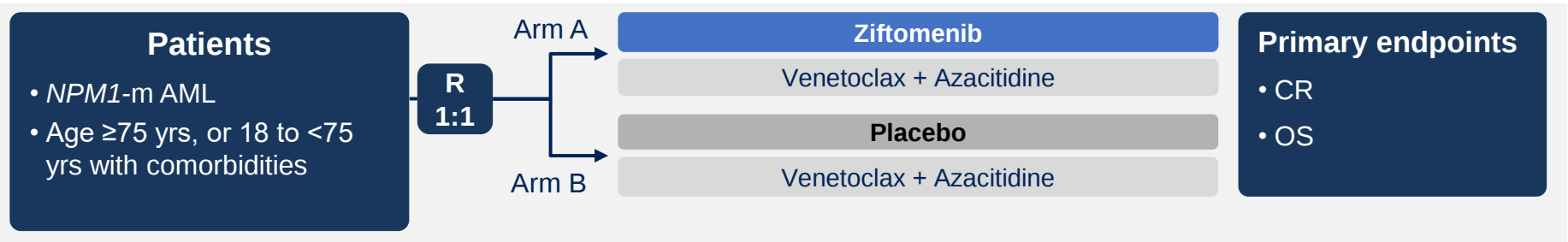
Conclusions

- **In the ongoing KOMET-007 study, ziftomenib 600 mg QD combined with Ven/Aza showed high rates of durable morphologic and MRD-negative CR in newly diagnosed *NPM1*-m AML**
 - 86% CRc (73% CR), with 68% molecular CRc MRD-negativity
 - Median duration of CRc and median OS were not reached as of the data cutoff
- **The addition of ziftomenib to Ven/Aza did not result in increased toxicity**
 - Myelosuppression was as expected for Ven/Aza
 - Times to neutrophil and platelet count recovery were comparable to those for Ven/Aza alone
 - One case each of differentiation syndrome (grade 2) and investigator-assessed QTc (grade 3) were successfully managed and did not require discontinuation of ziftomenib
- **Taken together, these data support advancement of this ziftomenib-based combination in the ongoing KOMET-017 ([NCT07007312](#)) randomized phase 3 study in newly diagnosed *NPM1*-m AML**

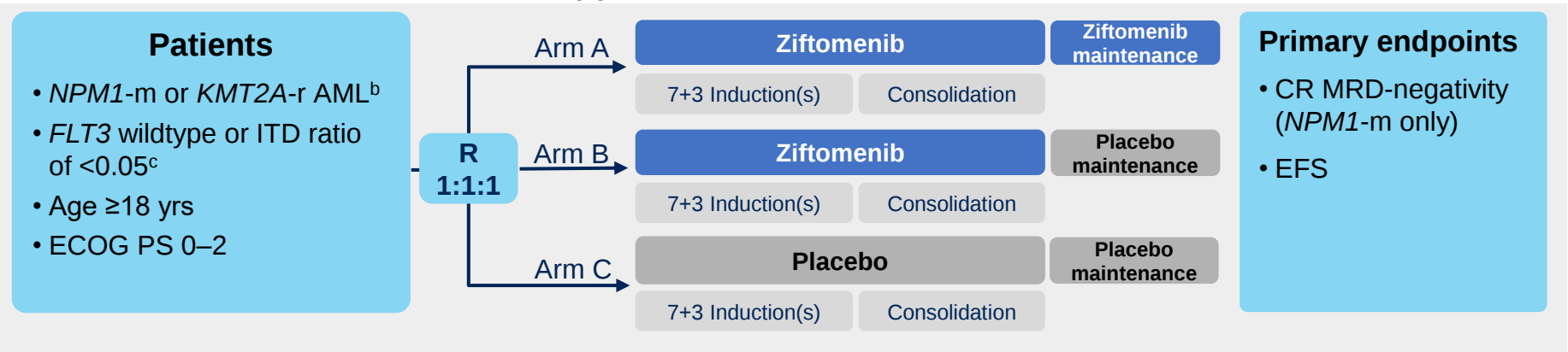
KOMET-017: Phase 3 Ziftomenib Pivotal Newly Diagnosed Combination Studies

Two independently powered, registration-enabling, randomized phase 3 studies in fit and unfit newly diagnosed AML (N=1300)

KOMET-017-NIC: Non-intensive therapy^a – Ziftomenib + venetoclax/azacitidine combo



KOMET-017-IC: Intensive therapy^a – Ziftomenib and 7+3 combo



Currently enrolling as of September 2025 ([NCT07007312](https://clinicaltrials.gov/ct2/show/study/NCT07007312))

^aHSCT allowed on both studies. ^bExcluding partial tandem duplication; ^cUnless ineligible for *FLT3*-targeted therapy

CR, complete remission; EFS, event-free survival; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; ITD, internal tandem duplication; MRD, measurable residual disease; NIC, non-intensive chemotherapy; OS, overall survival; R, randomized

Acknowledgments

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